unpatentable over applicant's previous U.S. Patent 4,113,881, which describes and claims only a method for treating rheumatoid arthritis with cetyl myristoleate. This ground of rejection is respectfully traversed.

In the outstanding rejection it is correctly asserted that applicant's previous patent mentions the use of cetyl myristoleate to treat or prevent "poly-arthritis." From this acknowledged teaching it is therefore concluded that the use of this compound to treat "non-rheumatoid arthritis" would have been suggested to the "skilled artisan". Respectfully, this conclusion is not correct, particularly with respect to the treatment of osteoarthritis as now claimed. As applicant has pointed out in the present specification there are over 100 different kinds of "arthritis", having different causes, symptoms, and, most importantly, treatment. The American Medical Association Encyclopedia of Medicine states at page 132 (attached Exhibit 1):

> Arthritis is not a single disorder but the name of joint diseases from a number of causes. The arthritis may involve one joint or many--

The AMA Encyclopedia further describes osteoarthritis as being the most common type of arthritis and resulting from "wear and tear on the joints". Rheumatoid arthritis is described as the most severe form of arthritis and as being an "autoimmune disorder in which the body's immune system acts against and damages joints and surrounding soft tissues". Rheumatoid arthritis is also a disease involving inflamation whereas osteoarthritis is not. Except that both diseases may effect the joints they have nothing in common. (See also attached Exhibit 2 at page 2, defining "arthritis", Exhibit 3, describing the symptoms and causes of osteoarthritis in considerable detail and Exhibit 4 which distinguishes rheumatoid arthritis from osteoarthritis).

The two diseases have nothing in common as to cause and there is nothing to suggest that using cetyl myristoleate to treat rheumatoid arthritis, as taught and claimed in applicant's earlier patents would lead one to use this material to treat osteoarthritis, as presently described and claimed.

Perhaps confusion has arisen from the term "poly-arthritis" used in the prior patent and referred to in the outstanding Office Action. Poly-arthritis does not mean all or many types of arthritis. As confirmed by Blakiston's New Gould Medical Dictionary at page 943 (Exhibit 5), "polyarthritis" merely means inflamation of many joints. The references in applicant's earlier patent was clearly to inflamatory rheumatoid arthritis effecting multiple joints, not osteoarthritis which is a distinctly different disease involving little or no inflamation (see Exhibit 3, page 3) which may or may not involve multiple joints. Applicant's earlier patent is concerned only with treating rheumatoid arthritis and nowhere mentions or suggests the treatment of osteoarthritis with cetyl myristoleate or anything else.

Clearly, the skilled artisan, knowledgeable in the meaning of the term "polyarthritis", and reading a patent dealing exclusively with inflamatory, rheumatoid arthritis would not be led by that patent's teaching to suppose that the same medication would be effective in treating a totally different disease, osteoarthritis which involves little or no inflamation.

In view of the present amendments and considerations advance herein, on reconsideration: allowance of this case is appropriate.

Respectfully submitted,

James J. Brown
Registration No. 24,808
Attorney for Applicant

(703) 448-1770 ext. 111
6667-B Old Dominion Drive
McLean, Virginia 22101

Dec. 22, 1995

Exhibit 1

THE AMERICAN MEDICAL ASSOCIATION

ENCYCLOPEDIA OF MEDICINE

MEDICAL EDITOR
Charles B. Clayman, MD

5569 676

Random House
New York

The information in this encyclopedia reflects current medical knowledge. The recommendations and information are appropriate in most cases; however, they are not a substitute for medical diagnosis. For specific information concerning your personal medical condition, the AMA suggests that you consult a physician.

The names of organizations, products, or alternative therapies appearing in this encyclopedia are given for informational purposes only. Their inclusion does not imply AMA endorsement, nor does the omission of any organization, product, or alternative therapy indicate AMA disapproval.

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A

Arthritis

Inflammation of a joint, characterized by pain, swelling, stiffness, and redness. Arthritis is not a single disorder but the name of joint disease from a number of causes. The arthritis may involve one joint or many, and can vary in severity from a mild ache and stiffness to severe pain and, later, joint deformity.

TYPES AND CAUSES

OSTEOARTHRITIS Also known as degenerative arthritis, this is the most common type of arthritis. It results from wear and tear on the joints, evolves in middle age, and most commonly troubles older people.

RHEUMATOID ARTHRITIS The most severe type of inflammatory joint disease, this is an *autoimmune disorder* in which the body's *immune system* acts against and damages joints and surrounding soft tissues. Many joints—most commonly those in the hands, feet, and arms—become extremely painful, stiff, and deformed.

STILL'S DISEASE Juvenile rheumatoid arthritis; it is most common in children under the age of 4. It usually clears up after a few years but even then may stunt growth and leave the child with permanent deformities.

SERONEGATIVE ARTHRITIS This is a group of disorders that causes symptoms and signs of arthritis in a number of joints, although blood test results for rheumatoid arthritis are negative. It can be associated with skin disorders (such as *psoriasis*), inflammatory intestinal disorders (such as *Crohn's disease*), or autoimmune disorders.

INFECTIVE ARTHRITIS Also known as septic or pyogenic arthritis, this is joint disease caused by the invasion of bacteria into the joint from a nearby infected wound or from *bacteremia* (infection in the bloodstream). The infected joint usually becomes hot as well as painful and swollen.

Arthritis in the hands
Severely deformed joints in the hands of an elderly woman who is suffering from rheumatoid arthritis.

Arthritis may also occur as a complication of an infection elsewhere in the body, such as *chickenpox*, *rubella* (German measles), *mumps*, *rheumatic fever*, or *gonorrhea*; it may also be a complication of *nonspecific urethritis*, in which case the joint inflammation forms part of *Reiter's syndrome*.

ANKYLOSING SPONDYLITIS In this arthritis of the spine, the joints linking the vertebrae become inflamed and the vertebrae fuse. The arthritis may spread to other joints, often the hips.

GOUT This disorder is associated with a form of arthritis in which uric acid (one of the body's waste products) accumulates in joints in the form of crystals, causing inflammation. It usually affects one joint at a time.

DIAGNOSIS

The diagnosis is made from the patient's symptoms and signs. To discover the cause, fluid may be withdrawn through a needle from an affected joint. This fluid may then be examined microscopically for the presence of microorganisms, or uric acid or other crystals. Sometimes a *culture* is made from the fluid so that it can be analyzed for any infection.

X rays may be carried out to reveal the type and extent of damage to joints. *Blood tests* can reveal the presence of proteins typical of rheumatoid arthritis, a high level of uric acid indicative of gout, or sometimes a high *ESR* (erythrocyte sedimentation rate), indicating inflammation.

TREATMENT

There are specific treatments for the different types of arthritis—for example, *antibiotic drugs* for septic arthritis, *anti-inflammatory drugs* for treating rheumatoid arthritis and osteoarthritis, and allopurinol for gout. Many other drugs are used to treat different forms of arthritis, but none seems able to effect a cure.

In a severe attack of arthritis affecting several joints, a few days' bed rest will help settle the inflammation; individual joints can be splinted to reduce the pain, and heat and supervised exercises help keep the deformity in the joints to a minimum. Obese people with arthritis in weight-bearing joints should lose weight.

Diseased joints that have become extremely painful, unstable, or deformed may require *arthroplasty* (replacement of the joint with an artificial substitute) or *arthrodesis* (fusion of the bones in the joint).

OUTLOOK

Arthritis has many forms and varies widely in its effects. Only a few sufferers become severely disabled. Most are able to lead productive lives, although activity may need to be altered to preserve joint function.

Arthrodesis

A surgical procedure in which the two bones in a diseased joint are fused to prevent the joint from moving.

WHY IT IS DONE

If pain and deformity in a diseased joint are so severe that they cannot be relieved by drugs, splinting, and physical therapy (as can occur in *rheumatoid arthritis*), or if a joint has become unstable, usually as the result of an injury, some form of surgery is required. In most cases, the operation of first choice is *arthroplasty* (reconstruction of a diseased joint using artificial replacements), since this procedure retains movement in the joint. When arthroplasty is not feasible or fails, arthrodesis is used.

HOW IT IS DONE

A local anesthetic may be all that is required for a small joint, such as a finger. Otherwise, general anesthetic is used. The technique of the operation varies according to the joint being treated, but in most cases cartilage (smooth, shock-absorbing tissue) is removed from the ends of the two bones, along with a surface layer of bone from each. The two ends are then joined so that, when fresh bone cells grow, the ends will fuse. The bones may need to be kept in position with plates, rods, or screws; a *bone graft* may also be carried out.

In arthrodesis of the knee or ankle, additional immobilization of the joint—by transfixing it with pins inserted through the skin—may be necessary to keep the area stable until healing is complete.

RECOVERY PERIOD

Complete union of the bones can take up to six months but is usually much quicker. In some cases the bones fail to fuse, but often this is irrelevant because fibrous tissue fills the gap between them and is strong enough to provide the same effect and strength as bone fusion.

OUTLOOK

One advantage of arthrodesis over arthroplasty is that, once performed, it needs no regular surveillance or further care; the patient can be reasonably certain that the problem with the joint has been solved permanently.

Exhibit 2

NATIONAL OFFICE
1212 Avenue of the Americas / New York 10036

33R

ARTHRITIS

THE ARTHRITIS FOUNDATION
1212 Avenue of the Americas
New York, New York 10036

No case is hopeless. Something can be done for arthritis now. Moreover, research for the cause and cure of arthritis is moving forward rapidly. New therapies and many promising new drugs are emerging. Yesterday's discouragement can be replaced by today's optimism.

Throughout the ages, rheumatoid arthritis has been one of the most painful crippling diseases affecting mankind. It has also been one of medical science's greatest puzzles. The mysteries of rheumatoid arthritis are slowly but surely being unravelled by research which now shows promise of bringing this great crippler under control.

We do not know the cause and we do not have a cure. Nevertheless, the painful and disabling effect of rheumatoid arthritis can be alleviated by modern medical skills. With early diagnosis and treatment of symptoms most of the severe crippling can be prevented. With new techniques for rehabilitation, even severely disabled persons can be brought back to a more active and productive life.

What arthritis is

The word arthritis literally means inflammation of a joint.

However, it is widely used to cover many different conditions which cause aching and pain in joints and connective tissues throughout the body, not all of them necessarily involving inflammation.

Rheumatism is a vague word used for unexplained aches and pains in joints and muscles. Even specialists in arthritic and rheumatic diseases don't agree on a precise definition. In Great Britain, for example, people use "rheumatism" to include most forms of arthritis. On the other hand, in the United States "arthritis" is the more common term, broadly used to cover rheumatism as well as other conditions.

Inflammation

The key thing that happens in the most serious forms of arthritis, inflammation—which shows itself as heat, swelling, redness and pain—is the way the body reacts to injury, the way it reacts when something is damaging body tissue. In arthritis, inflammation itself is damaging to tissue.

Chronic Disease

It is extremely important to understand that the major forms of arthritis are chronic. This means the condition, once started, continues, usually for life. It means that whatever damage takes place remains permanently . . . and tends to get worse unless proper precautions are taken to prevent it.

Common Forms of Arthritis

The five most widespread kinds of arthritis, with explanations of how they are different, are:

Rheumatoid arthritis. This is the most serious, the most painful, the most crippling. Inflammatory and chronic, it can affect the whole body. Primarily it attacks the joints, but it can also cause disease in the lungs, skin, blood vessels, muscles, spleen, heart and even the eyes. In children it occurs in a form known as juvenile rheumatoid arthritis.

Osteoarthritis. Also called degenerative joint disease, this is principally a wear-and-tear disease of the joints which comes with getting older. It is usually mild and is not generally inflammatory. It does not cause general illness. Sometimes there can be considerable pain. Mild to severe disability may develop gradually.

Ankylosing spondylitis. This is chronic inflammatory arthritis of the spine. It affects men ten times as often as women, usually beginning in the teens or early twenties.

Rheumatic fever. This is an acute disease which follows a streptococcus infection. It frequently damages the heart. It also causes arthritis which usually subsides quickly without crippling.

Gout. Also called gouty arthritis, this is an inherited disease which most often attacks small joints, especially the big toe. Most victims are men. It is intensely painful.

What are the chief symptoms of rheumatoid arthritis?

Rheumatoid arthritis usually begins with general fatigue, soreness, stiffness and aching followed by the gradual appearance of localized symptoms in a joint or in several joints consisting of pain, swelling, warmth and tenderness. Sometimes there is a sudden onset of these joint symptoms. In most cases several joints become involved, particularly those of the hands and feet.

Usually there is weakness and fatigue, also loss of appetite and loss of weight. Frequently patients have cold, sweaty hands and feet.

The symptoms may leave or return with flare-ups and periods of improvement.

Gradually, joint motion can be lost and in time deformities of the joints may occur.

In addition to joint symptoms patients may have other changes such as lumps or nodules under the skin, inflammation of the eyes, pleurisy and anemia.

How is rheumatoid arthritis detected?

A physician must make the diagnosis. He will review carefully all of the patient's complaints including symptoms that might have occurred far back in the past. He will perform a general examination and give special attention to the joints, noting signs of inflammation, losses of motion or any other abnormalities of each joint. In addition, he will want blood and other chemical tests and perhaps X-rays to determine the condition of bones and joints.

The doctor then studies all the information he has, including the patient's complaints and his findings on examination, the results of X-ray and laboratory work, and from the overall pattern —not from any one symptom—he makes the diagnosis. Continued observation over a prolonged period of time may be necessary to make a proper diagnosis.

Are there special tests for rheumatoid arthritis?

Yes. Doctors perform several blood tests which can help make

the diagnosis. Tests for rheumatoid factor, a complex protein circulating in the blood of many persons with rheumatoid arthritis, may be performed. These tests are called by several names, such as latex test, sheep cell test, bentonite test. They are not always conclusive, but may be helpful in confirming a diagnosis.

Another useful test is the sedimentation rate, which measures the speed of settling of red blood cells to the bottom of a small tube. Where chronic inflammation exists the cells settle more rapidly than is normal. Rheumatoid patients usually have fast sedimentation rates.

Blood counts are done when the patient is first examined, also at frequent intervals when certain treatments are used. Mild anemia occurs in many cases. Urine tests also are taken. At times, analysis of joint fluid may be necessary to look for the kind of arthritis a patient may have—rheumatoid, osteo or joint pain related to other diseases. The fluid can be removed quite easily and painlessly by tapping the joint with a needle. Also, on occasion small pieces of inflamed joint tissue or nodules may be removed by a doctor and examined under a microscope. This procedure, called a biopsy, is safe and can be performed with very little discomfort to the patient.

Are X-rays important?

Yes, but not always. Sometimes the physician can make a diagnosis without them and will only request X-rays of certain joints to answer specific questions. In other instances X-ray examination may be needed to help make a diagnosis or for follow-up studies to determine if the illness is progressing and also what damage has been done to the joints.

Does rheumatoid arthritis affect men and women equally?

No, it is seen more often in women than in men. It is most likely to strike people from 20 to 50, but can occur at any age. Children sometimes suffer from rheumatoid arthritis, either in a rather mild form or in a serious and fast-developing form which is also called Still's disease.

Does rheumatoid arthritis always do lasting harm?

Probably yes, but in most instances the amount of permanent damage in rheumatoid arthritis is very small during the early years of the disease and if it is kept under control. However, there is always some tissue inflammation even when it cannot be detected by X-ray. In more serious forms, there may be erosion of the cartilage and bones and scarring of the soft tissues around the

joint. Sometimes in severe cases joint surfaces are affected to the point where the joint cannot bear weight or is unstable, and in other cases the joint surfaces actually grow together so they cannot be moved. For every patient who may have serious crippling or deformities, however, there may be hundreds who don't even realize their aches and pains are caused by rheumatoid arthritis.

Does rheumatoid arthritis ever go away?

Yes, at least as far as the patient can tell. It is typically a disease of ups and downs. It is quite common even for a person with severe rheumatoid arthritis to have periods lasting weeks, months or years, in which pain and stiffness are much reduced and even absent. These periods of easing off are called remissions, and may appear suddenly and unexpectedly. Sometimes the rheumatoid arthritis seems to disappear completely. This happens in about one out of every five cases. Doctors may still find evidence that the disease is present but, so far as the patient is concerned, it has disappeared.

What causes rheumatoid arthritis?

No one knows. There are two leading theories held by many scientists but neither of them has been proved.

First, some scientists believe that rheumatoid arthritis may be caused by a virus of some kind. But research over a period of many years in laboratories and in many hospitals has not yet proven definitely that any germ is responsible for the disease. If rheumatoid arthritis were caused by a virus, one would expect to find it in the affected joints. But none has been found regularly there.

Second, many scientists think rheumatoid arthritis may be caused by a derangement of the body's own defense, or immune, mechanism. The idea is that in some complicated way the body's chemistry is thrown out of kilter so that the body produces antibodies which attack its own joints and tissues. The suspected process is known as autoallergy. This theory of autoallergy is yet to be proved, but is considered likely to be an important factor by many scientists in the field. Some now suggest that perhaps an infection triggers a chain of events leading to autoallergy, even though the virus itself may be gone by the time the disease develops.

At one time it was thought that rheumatoid arthritis might be caused by some kind of hormone difficulty. Women who have rheumatoid arthritis generally feel much better during pregnancy. Since the body produces markedly increased amounts of certain glandular secretions called hormones during pregnancy, it was natural to suppose that rheumatoid arthritis might be the result

of a hormone condition. But the hormones currently known to be produced during pregnancy do not cure rheumatoid arthritis and hormone preparations which have an effect on the inflammation caused by the disease are not quite the same as those produced in pregnant women.

Can emotional upsets cause rheumatoid arthritis?

No one is certain of the importance of emotional stresses in causing rheumatoid arthritis, but it seems clear that worry may be an important factor in aggravating the disease in certain individuals. Many patients notice the beginning of symptoms following a disturbing event such as a death in the family, divorce, separation, or an emotional strain or shock. In patients who already have rheumatoid arthritis, such events may seem to make the disease worse. Even worrying unrealistically about having arthritis sometimes seems to delay improvement. It is also noticed that when emotional stresses are relieved, improvement follows. Patients can help themselves a great deal by discussing their personal problems frankly with the doctor.

Is it absolutely necessary to find the cause? Isn't it possible that a cure or preventive might be found even before the cause of rheumatoid arthritis is proved?

Yes, it is possible. Smallpox vaccine, which is very effective, actually was developed long before scientists had a clear idea of what caused smallpox. But it is more likely that a cure or preventive for rheumatoid arthritis can be found if doctors first can learn exactly what causes the disease and how it develops. Much has been done already, of course, and present treatment methods, while they do not constitute a cure can, in most cases, relieve pain and suffering, prevent and correct deformities and, possibly, shorten attacks far more effectively than measures used only a few years ago.

What is the treatment for rheumatoid arthritis?

Each case of rheumatoid arthritis is individual and different from all others. Therefore, there is no single pattern of treatment that is used for every patient with rheumatoid arthritis. What the doctor recommends will depend on how severe the disease is, what joints are affected, the nature of general symptoms, the patient's age and occupation and even his or her family life.

No Wonder Drug, No Magic Cure

The wonder drug age of medicine has made many people think that for every ailment there ought to be one pill or injection that will solve the problem. It would be fine if this were so, but it is not. There is no single drug that will cure rheumatoid arthritis. There is no magic pill and no magic injection.

Rheumatoid arthritis is one of a number of increasingly important chronic illnesses for which treatment generally involves doing a number of things, instead of just one or two.

The Patient's Whole Life Involved

When a doctor sees the patient therefore, he may want to know how he lives, and a great many things that might, at first glance, seem a little removed from the problem of the illness. They aren't really removed; they are very much a part of the picture. Worry, to an abnormal degree, also can have an important bearing on the course of the rheumatoid arthritis.

A Variety of Things Can Be Done

The doctor may want to know about family life, about job activities, whether the patient has adequate rest, both physical and mental, for instance. He is quite likely to prescribe some kind of exercise or physical therapy, because this has proved very useful in arthritis. Indeed, the right balance of special exercise and rest is important in treatment. The doctor is likely to inquire into diet, not because any diet can cure rheumatoid arthritis—none can—but because good, sound nutrition is helpful. He may prescribe one or more drugs. These do not cure the arthritis, but may help reduce inflammation and pain. There are many things the doctor can do to help the patient maintain an active, productive life despite his disease.

What drugs are used in rheumatoid arthritis?

There are many that may be prescribed. When the doctor prescribes one of them, it is because he feels there is a particular reason for it. Just because some other person with rheumatoid arthritis is receiving a certain drug does not mean that every patient needs it or would benefit from it. Some people, furthermore, react adversely to certain drugs. In this case, the doctor will naturally want to prescribe other drugs to which the patient is not sensitive.

What about aspirin?

Aspirin is the single drug most widely used in the treatment of rheumatoid arthritis. It is a member of a family of chemicals called salicylates. The word salicylate comes from "salix," the Latin name for willow, and the bark of willow trees is a source of such chemicals, although today they are generally produced synthetically. The common name, aspirin, comes from "spirin," meaning spirea plant, which was one early source for the drug.

Exhibit 3

NATIONAL HEADQUARTERS
1212 Avenue of the Americas / New York 10036

OSTEOARTHRITIS

THE ARTHRITIS FOUNDATION

THE ARTHRITIS FOUNDATION
1212 Avenue of the Americas
New York, New York 10036

Introduction

Osteoarthritis is man's oldest and most common disease. Beginning at least with dinosaurs, almost every animal that can walk has been susceptible to arthritis. As a human affliction, it is certain that every person over 60 could be found to have it to some degree. Only a small percentage of those with osteoarthritis have it badly enough to notice it, but when it is troublesome something has to be done about it and proper medical treatment is necessary.

Although osteoarthritis can cause severe pain and sometimes physical disability, it cannot be called a bad disease. It can't be prevented or cured, but the symptoms can usually be alleviated and the more serious physical handicaps prevented or corrected.

The purpose of this booklet is to explain in simple terms what osteoarthritis is, how it causes trouble and what can be done about it.

WILLIAM E. REYNOLDS, M.D.
Director of Medical & Scientific Affairs
The Arthritis Foundation

DESCRIPTION

Who has osteoarthritis?

An estimated forty and a half million Americans, or 37 out of every 100 adults, have osteoarthritis. About ten million of them have it seriously enough to cause painful problems. Ninety-seven per cent of all people over 60 show signs of the disease.

The occurrence of osteoarthritis increases with advancing years. When all ages are considered, men are as frequently affected as women. But in people under age 45, more than twice as many men as women have it; and between 55 and 65, more women than men have it. In the above-65 group there is hardly any difference.

What is osteoarthritis?

Put simply, it is a disease of the joints that involves a breakdown of cartilage and other tissues which make a movable joint operate properly. The damage from osteoarthritis is confined to the joints and surrounding tissues. There is little or no inflammation, but pain and limitation of normal motion sometimes occur.

Osteoarthritis is often described as a wear-and-tear disease. It frequently is just that—but not always.

Does osteoarthritis have other names?

Yes, several. A common label for osteoarthritis in recent years has been "degenerative joint disease." Some physicians also call it arthrosis, osteoarthrosis, and hypertrophic arthritis. Osteoarthritis in certain joints has special names.

What other kinds of arthritis are there?

There are many forms of arthritis—often referred to collectively as the rheumatic diseases, or just plain rheumatism. The most prevalent, in addition to osteoarthritis, are rheumatoid arthritis, ankylosing spondylitis, rheumatic fever and gout. Each is a distinct disease and has a different effect on the patient. Rheumatoid arth-

ritis causes the most trouble and can strike at any age; its victims include infants and children, young adults and even the elderly. Osteoarthritis is the most common of all and is not directly related to other types.

Arthritis patients often confuse osteoarthritis with rheumatoid arthritis. The thing to remember is that rheumatoid arthritis causes inflammation of the joints and can affect the whole body, including internal organs. Osteoarthritis does not affect the whole body and seldom causes inflammation.

What are the tissues that make joint motion possible?

The movable joints, particularly those in the arms, legs, shoulders, hips and spine, allow intricate motions of the various parts of the skeleton. Each joint contains specialized tissues which connect bones and permit movement between them.

The ends of the bones in a joint are contoured to fit snugly together. The end of each bone is covered with a layer of smooth rubbery gristle, called cartilage. The joint cartilage acts as an elastic cushion and with proper lubrication permits smooth motion between the bones.

In all joints the ends of bones are fastened together by sheets and strands of dense fibers called ligaments. And each joint is completely enclosed by a capsule of ligament tissue.

The capsule is lined by a membrane which secretes fluid into the space between the bones to lubricate the joint. This slippery liquid is called synovial fluid. There is no oil in the joint.

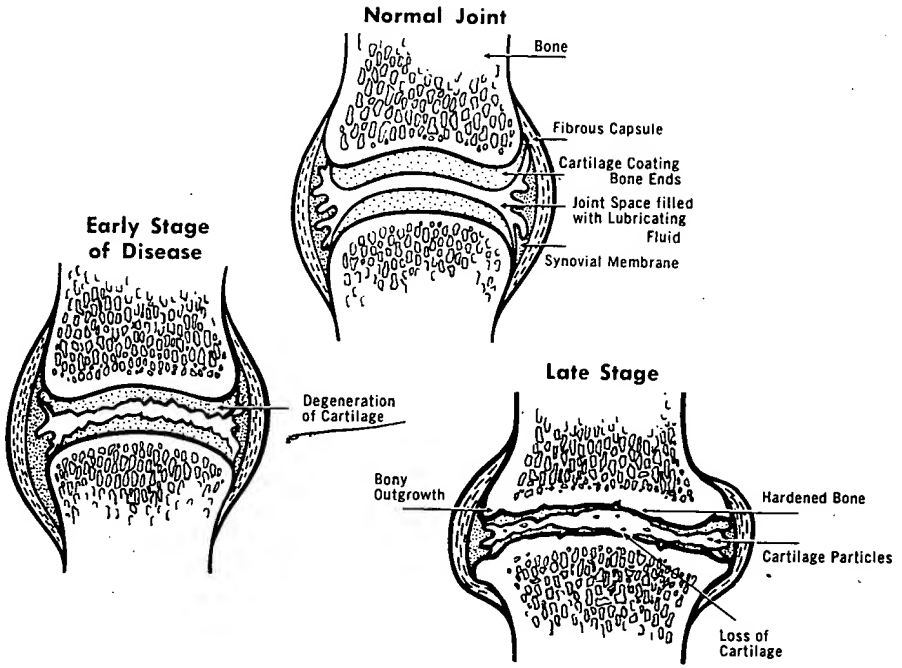
What happens to joint tissue in osteoarthritis?

The first noticeable change is a softening, pitting and fraying of the smooth cartilage surface. It loses its elasticity and becomes more susceptible to further damage due to stress.

As the disease progresses, whole sections of cartilage may be worn away completely, leaving only smooth bone ends exposed to each other. When the gliding surfaces of normal cartilage are gone, it may become painful to move the joint.

As cartilage disintegrates, the joint begins to lose its normal shape, the underlying bone ends become thickened and bony spurs may form where the ligaments and capsule are attached. Cysts may form in the bone near the joint and fragments of bone or cartilage can become loose within the joint.

In very severe osteoarthritis, the normal shape and mechanical structure of a joint may be destroyed.



In what joints does osteoarthritis occur?

Strictly speaking, osteoarthritis can occur in any joint. Certain joints are more prone to become involved than others. Some seem to be spared except when they have been injured.

The most commonly involved joints are those that bear weight such as the hips, knees and spine. Also involved frequently are the terminal joints of the fingers and joints at the base of the thumb and big toe. Osteoarthritis can be troublesome sometimes in the joints of the jaw and in the second row of finger joints.

This condition seldom affects the base of the fingers, the wrists, elbows, shoulders or ankles, except when these joints are previously diseased or injured or are subjected to repeated strains as may occur in athletics or in certain occupations.

Is there more than one kind of osteoarthritis?

Yes. Doctors tend to separate the condition into two kinds, sometimes called "primary" and "secondary" osteoarthritis. This is because the disease can start by itself, so to speak, without any apparent triggering cause or event; this is the primary kind. The

other type seems to result from wear and tear on or injury to the joints—and gets its name from the fact that the condition is "secondary" to, or the result of, such stresses and strains.

Do primary and secondary osteoarthritis behave differently?

They seem to. Primary osteoarthritis is more generalized, occurs mostly in women and affects small joints, especially in the fingers and toes. It occurs somewhat earlier in life, occasionally even in the late thirties and early forties, and seems to be more common in some families than in others.

Secondary osteoarthritis tends to affect the larger joints and may hit small joints which are more exposed to excessive stresses and strains. It occurs late in life as a rule, but can occur early when a particular joint is badly abused.

Can one person have two kinds of arthritis?

Yes. For example, it is not uncommon for an individual to have rheumatoid arthritis and osteoarthritis at the same time. This is sometimes called "mixed arthritis." It happens because chronically inflamed joints, such as those in rheumatoid arthritis, are prone to the development of secondary osteoarthritis.

Do certain occupations lead to special kinds of osteoarthritis?

In a sense, yes. The pattern in which joints are affected is often related to the particular physical stress and strain of a particular occupation. A baseball pitcher is more likely to develop osteoarthritis in his throwing arm, especially in the elbow. A football player may get osteoarthritis in his knees. Ballet dancers have been known to get osteoarthritis of the ankles. These are examples of the "wearing out" of specific joint tissues by excessive use.

What causes osteoarthritis?

Nobody knows. Heredity may be a predisposing factor, particularly in the primary type. In secondary osteoarthritis, a joint may become involved simply because it receives more punishment than it can take. Overweight people may be more susceptible to osteoarthritic involvement.

Scientists still would like to know, however, why some people

get osteoarthritis more readily than others, and why some have rather severe osteoarthritis at a relatively early age while others go through life with almost no trouble at all.

The leading theory is that some people have better cartilage than others and that chemical abnormalities may be present in those who get osteoarthritis.

Another theory is that some people are born with mechanical imperfections in their joints which are not noticeable but cause the joint to wear out sooner.

With what is now known, it seems logical that a joint which does not function perfectly, whether because of hereditary factors or because of an injury, will be more prone to osteoarthritis.

SYMPTOMS - DIAGNOSIS

What are the symptoms of osteoarthritis?

As mentioned previously, many people with osteoarthritis are not bothered by it even though there may be visible evidence of it. When there is trouble, the number one symptom is pain. Most patients experience only mild aching and soreness, particularly with movement. Some patients may have constant nagging pain which will persist even at rest.

The second most common symptom is loss of mobility. This usually is noticed as inability to perform easy, comfortable movements of the joints involved. Severe loss of motion is unusual but it can occur to the point where a joint is completely stiff.

With soreness and loss of joint mobility, the muscles serving the joint become weakened and overall body coordination and posture may become affected.

The pain of osteoarthritis may be confined to the joint area or it may spread to the general part of the body involved. In rare instances the pain may be felt some distance from the involved joint. In this case it is called "referred" pain. For example, an osteoarthritic hip may produce pain in the region of the knees.

What causes osteoarthritis pain?

The pain is caused by irritation and pressure on nerve endings, muscle tension and muscle fatigue. Pain in osteoarthritis is not always related to the amount of damage that has been caused in the joint. Sometimes a patient with a joint that is severely affected by osteoarthritis may have less pain than a patient with a joint that seems only mildly affected.

Usually, although not always, joints affected by osteoarthritis are most painful after overuse. On the other hand, joints may be especially painful when first moved after a long period of inactivity.

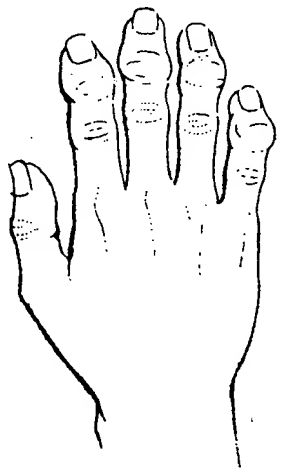
What other symptoms are there?

Osteoarthritis is noted for *absence* of what doctors call "generalized" symptoms, meaning symptoms of sickness. There is no fever, no loss of weight and patients don't feel sick. In fact, the lack of sickness symptoms helps doctors to make the correct diagnosis. Of course, muscle weakness can progress to a point where general weakness occurs simply from lack of exercise.

It is true, however, that in unusual circumstances the referred pain of osteoarthritis, particularly of osteoarthritis of the spine, can resemble the pain of diseased internal organs.

What are Heberden's nodes?

These are bony enlargements of the end joints of the fingers. They are most often observed in primary osteoarthritis in women, sometimes appearing as early as age 40. There is a tendency for Heberden's nodes to run in families.



Heberden's Nodes

Similar enlargements of the middle joints of the fingers are often called Bouchard's nodes.

Both Heberden's nodes and Bouchard's nodes are commonly associated with primary osteoarthritis, although either may result from an injury to the finger such as "baseball finger" or "bowler's finger."

Typical Heberden's nodes are multiple, appearing in one finger and spreading to other fingers. These nodes may be painless, but in some cases they appear rather suddenly with redness, swelling, tenderness and aching. Patients with Heberden's nodes may complain of numbness and tingling of the fingertips and clumsiness of the hands.

Although osteoarthritis of the hands associated with enlargement of the finger joints can be painful and unsightly, good function of the hands can be maintained and significant crippling is not likely to occur.

What should someone who suspects osteoarthritis do?

He should see a qualified physician. Only by consulting a doctor can he find out if painful joints are caused by osteoarthritis or something else. Since many people have some mild osteoarthritis that is not causing trouble, it is obvious that everyone with this affliction does not need medical care. Nevertheless, joint symptoms can be caused by a number of ailments and when they occur a proper diagnosis should be made and appropriate treatment begun.

How does the doctor recognize osteoarthritis?

In most instances a careful analysis of symptoms and thorough examination of the affected joints gives the doctor a fairly good idea of what the problem is. When there is substantial joint involvement, special tests may be necessary both to confirm the diagnosis and to determine how serious the problem is. Often these additional examinations are useful in ruling out other types of arthritis.

What special tests are used in diagnosing osteoarthritis?

Probably the most valuable are x-ray examinations. These show rather typical changes which help the doctor to make his final diagnosis.

A useful test is called the sedimentation rate test. This measures how fast red blood cells settle to the bottom of a small tube. The red blood cells from a person with chronic inflammation settle more rapidly than normal. Osteoarthritis patients without complicating illnesses have normal sedimentation rates.

Sometimes blood counts are done when the patient is first examined, and also at frequent intervals when certain treatments are being used. Occasionally a detailed analysis of joint fluid may be extremely important. Presence of this fluid in excess amounts, sometimes called "water-on-the-joint," causes the joint to swell. The fluid can be removed quite easily and painlessly by tapping the joint with a needle.

TREATMENT

What can be done for patients with osteoarthritis?

It is important to remember that osteoarthritis is not a disease that can be cured. But its symptoms *can* be alleviated and deranged joint function *can* be improved.

Exhibit 4

Brown and Scammell The ROAD BACK

EVANS

The ROAD BACK

RHEUMATOID ARTHRITIS— ITS CAUSE AND ITS TREATMENT

Thomas McPherson Brown, M.D., and Henry Scammell

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decade that it began at last to find its way back to the main road.

RETURNING TO THE MAIN ROAD

When an inexperienced hunting dog is first exposed to game, he uses all of his energy searching for tracks in an open field, running in circles, chasing after every lead regardless of how fresh or stale. A researcher in the cause of arthritis is faced with the same apparently endless number of possibilities, with the potential for at least as much frustration and hopelessness. But like the hunting dog, he eventually learns which directions are most likely to be productive and he begins to establish a set of priorities. And he starts to get results.

This book describes how the dogs that have been hunting for the infectious cause of arthritis eventually got smart, what they found, and why they are now about to become the Most Popular Breed.

It deals with all the rheumatoid forms of arthritis, which means every form except osteoarthritis. With that single exception, all the many and varied types of this affliction have an inflammatory component, they all show evidence of connective-tissue damage, and they all are under the aegis of a process which resembles the autoimmune reaction.

A real autoimmune reaction is the body fighting its own cells. In rheumatoid arthritis, the body does not attack its own cells as the primary target. What is called the autoimmune reaction in all these forms of arthritis is actually the body's natural defense against an infection in the connective tissues. The body attacks disease agents that cling to the cells or are embedded within them. The infectious agent, and the body's reaction, cause the inflammation, the pain, and the eventual disfigurement of rheumatoid arthritis. When the body makes that response, it also attacks the cell to which the disease

year. Just a couple of years ago it was 34 million, and now it has risen to 37 million. About half those people suffer from straight rheumatoid arthritis, and if you add in the patients who are afflicted with a combination of rheumatoid and osteoarthritis, the number is at least 25 million.

OSTEOARTHRITIS IS DIFFERENT

Osteoarthritis is a noninflammatory form of arthritis that is hereditary and is considered to be incurable. It is characterized by calcium deposits which can accumulate on pressure points and impinge on nerves, so there is some pain associated with it, although it is different from the pain that goes with the rheumatoid form. I have found that as a rule, when an osteoarthritis patient complains bitterly about the disease, it is because there is a component of rheumatoid arthritis mixed in with it. Until fairly recently it was very difficult to demonstrate the presence of rheumatoid arthritis in that kind of combination, because the osteo obscured the picture. However, the bone and joint scan has greatly illuminated the picture in recent times by revealing inflammatory reactions associated with the calcium pressure points.

This population of perhaps 10 million arthritics who have both forms represents a major added challenge, because a safe method of treatment is needed to allow the physician to probe therapeutically. It makes no sense to probe a possible combination of osteo and rheumatoid with gold or penicillamine or Plaquenil because the drugs are so dangerous to begin with. Until the bone scanner came along, many physicians chose to deal with the problem by concluding it wasn't there: they said that there was no such combination, and that a patient had either osteo or rheumatoid but never both. We have found through our own use of the bone scanner and tests for the mycoplasma antibody that approximately half the cases of osteoarthritis involve some degree of the rheumatoid form.

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Exhibit 5

Blakiston's NEW GOULD MEDICAL DICTIONARY

A modern comprehensive dictionary of the terms used in all branches of medicine and allied sciences, including medical physics and chemistry, dentistry, pharmacy, nursing, veterinary medicine, zoology and botany, as well as medicolegal terms; with illustrations and tables

EDITORS

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Arthur Osol, Ph.D.

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ı·ceph"a·li'tis [*polios;* G. *myelos, halos;* *-itis*, inflammation]. Polio- ɔlioencephalitis existing together. tis [*polios; myelos; -itis*]. 1. A com- ɔase of man which usually runs a ve course, characterized by upper d gastrointestinal symptoms, but gress to involve the central nervous sult in a nonparalytic or paralytic sease, the latter being the classical anterior poliomyelitis. It is endemic flare-ups. 2. Formerly, any inflam- e gray matter of the spinal cord. t'ic, *adj.*

n early form, diagnosed by inference demic, characterized clinically only mild symptoms of upper respiratory dache, gastrointestinal disturbances, omiting, but which does not progress nt of the central nervous system. nosis rests upon isolation of the virus al reactions.

ior p. An acute inflammation of the ıs of the gray matter of the spinal ıost common in children, producing certain muscle groups or of an entire nset is sudden, with fever, gastro- mplaints, and pain in the affected the paralysis is usually most exten- beginning, a certain amount of im- taking place subsequently. The scles atrophy rapidly, the reflexes in ios, and reaction of degeneration From contraction of antagonistic formities occur later in life. Also *ntile paralysis, epidemic paralysis, g paralysis, Heine-Medin's disease.*

ɔinal p. Anterior poliomyelitis, acute

p. A type similar to Landry's paraly- aralysis starts in the toes, rapidly the legs, thighs, trunk, and finally to s of respiration.

A form in which lesions are concen- he medulla of the brain; motor cranial respiratory and circulatory center ected.

ıal p. A form involving the medulla and l.

ınterior p. See progressive muscula

itic p. That in which, in addition to d spinal lesions, there is more diffuse nt of the brain. Principal symptoms in iety, hyperexcitability, signs of upper ıron lesion, muscular tremors, delirium, l occasionally convulsions.

p. A form of toxic neuritis due to metal where the paralysis is so severe that it poliomyelitis.

p. A type characterized by pain in the domen, and sometimes the lower limbs, araplegia, sensory loss extending to the ıd retention of urine. The end result araplegia and sphincter disturbances.

ılytic p. A form generally characteris and stiffness in the muscles of the axia especially of the neck and back, mild nd often increased amounts of protein nber of leukocytes in the cerebrospina his may be the clinical maximum of th Definitive diagnosis rests upon isolatio irus and serological reactions.

ːic p. A form with a variable combinatio of damage to the central nervous system ıg flaccid paralysis, weakness, incoordin

tion, muscle spasms, muscle tenderness, hyperesthesia, and disturbance of consciousness: subdivided, on the basis of anatomical structures involved, into acute anterior or spinal, bulbospinal, bulbar, and encephalitic types.

spinal p. See acute anterior *p.*

spinobulbar p. See bulbospinal *p.*

syphilitic p. See syphilitic *amyotrophia.*

po'li·o·my"e·lop'a·thy [*polios; myelos;* G. *pathos*, disease]. Disease of the gray matter of the spinal cord and medulla oblongata.

po'li·o·plasm" (po'lee·o·plaz"um) [*polios;* G. *plasma*, anything formed]. Granular cytoplasm.

po'li·o'sis [*polios;* G. *-ōsis*, condition]. A condition characterized by the absence of pigment in the hair. Syn., *canities.*

po'li·o·thrix. See *canities.*

Po'lish plait. See *plica* polonica.

Politzer, Adam [*Austrian otologist*, 1835–1920]. Described otosclerosis (1895). Introduced a method of testing hearing. A tuning fork held in front of the nares will be heard only by an unaffected ear during swallowing; called *Politzer's test.* See also Politzer *bag.*

po·litz"er·i·za'tion (po·lit"sur·i·zay'shun, ·eye·zay'shun, po"lit·sur·, pol"it·sur·) [*Politzer*]. The production of sudden increased air pressure in the nasopharynx to inflate the middle ear, by means of compression by a Politzer bag.

poll (pole) [ME. *pol*]. *In veterinary medicine*, that part of a horse's neck lying just posterior to the occiput.

Pollak's test. See von Jaksch-Pollak's *test.*

pol"la·kl·u'ri·a (pol"uh·kee·yoor'ee·uh, ·kigh·yoor'ee·uh) [G. *pollakis*, often; *ouron*, urine]. Abnormally frequent micturition.

pol·lan'tin [L. *pollen*, fine flour; G. *anti*, against]. A hay-fever antitoxin obtained from the blood of horses inoculated with pollen extract. Also called *Dunbar's serum.*

pol'len [L.]. The fecundating element produced in the anthers of flowering plants.

pol"le·no'sis [*pollen;* G. *-ōsis*, condition]. Hay fever or asthma caused by contact with pollen to which the patient is specifically sensitive.

pol'lex [L.]. The thumb. —**pol'li·cis,** *adj.*

p. valgus. A thumb abnormally bent toward the ulnar side.

p. varus. A thumb abnormally bent toward the radial side.

Pollister method. See Mirsky-Pollister *method.*

pol·lu'tion [L. *pollutum*, from *polluere*, to defile]. 1. The act of defiling or rendering impure, as pollution of drinking water. 2. The discharge of semen without sexual intercourse, as in nocturnal emission.

nocturnal p. A nocturnal, involuntary seminal discharge. *Obs.*

self-p. Masturbation. *Obs.*

po'lo·cyte [L. *polus*, pole; G. *kytos*, cell]. One of the small cells or bodies formed during the maturation divisions of the ovum. Syn., *polar body.*

po·lo'ni·um [ML. *Polonia*, Poland]. Po = 210. The first radioactive element isolated by Pierre and Marie Curie from pitchblende (1898); a product of disintegration of radium. Syn., *radium-F.*

pol·toph'a·gy [G. *poltos*, porridge; *phagein*, to eat]. Complete chewing of the food before swallowing it.

po'lus [L.]. A pole.

pol'y- [G. *polys*, many]. 1. A combining form meaning *much* or *many.* 2. *In medicine*, a combining form denoting *excessive, affecting many parts,* or *of diverse origin.*

Pólya, Eugene [*Hungarian surgeon*, 1876–1944]. Distinguished for his important contributions to the technic of gastrointestinal surgery. His gastroenterostomy is accomplished by the use of small Payr clamps placed upon the duodenum after freeing it with the pyloric end of the stomach, the duodenum being divided, the stomach retracted, and the duodenum closed. The stomach is clamped at a point distal to the freed portion in which all vessels have been secured. A loop of jejunum is brought through an opening in the transverse mesocolon and united to the posterior wall of the stomach, forming a posterior gastroenterostomy. Called *Pólya's method, Pólya's operation.*

pol"y·ac'id (pol"ee·ass'id) [G. *polys*, many; L. *acidus*, sour]. Applied to a base or basic radical capable of yielding two or more hydroxyl groups, as $Ba(OH)_2$, $Fe(OH)_3$.

pol"y·aes·the'si·a (pol"ee·ess·thee'zhuh, ·zee·uh). See *polyesthesia.*

pol"y·am'ine (pol"ee·am'in, pol"ee·uh·meen'). Nonspecific term referring to compounds possessing two or more amine groups.

pol"y·am'ine-meth'yl·ene res'in. Generic name for a synthetic acid-binding resin obtained by the polymerization of an aromatic amine and formaldehyde or of a polyamine, a phenol, and formaldehyde. Such a resin is useful clinically as a gastric antacid and to prevent acidosis when carbacrylic resin is used for its sodium-depleting effect. Also called *polyamine-formaldehyde resin.* See also *carbacrylamine resins.*

pol'y·an"dry [*polys;* G. *anēr*, man]. A social state in which is recognized the marriage of one woman with more than one man at the same time.

polyansyn. Trade-mark for a sterile solution of the various anterior pituitary factors.

pol"y·ar"te·ri'tis [*polys;* G. *artēria*, artery; *-itis*, inflammation]. Inflammation of a number of arteries at the same time.

p. nodosa. An acute and sometimes recurrent disease of unknown cause, frequently fatal and occurring at any age. The characteristic lesion is an irregularly distributed segmental panarteritis resulting in nodules and hemorrhage along the involved arteries. Histologically necrosis, edema, and cellular exudate, frequently including eosinophils, make up the lesions. It has been regarded by some as a reaction of hypersensitivity, and is grouped as a collagen disease. Also called *periarteritis nodosa, disseminated necrotizing periarteritis.*

pol"y·ar'thric [*polys;* G. *arthron*, joint]. Pertaining to many joints.

pol"y·ar·thri'tis [*polys;* G. *arthritis*, arthritis]. Inflammation of many joints, sometimes used to mean acute rheumatic fever.

epidemic tropical acute p. A self-limited syndrome of unknown cause, first described among Australian soldiers (1942), characterized by acute polyarthritis, mild fever, lymphadenopathy, and transient rash: also called *fox-hole arthritis, Bougainville rheumatism.*

pol"y·ar·tic'u·lar [*polys;* L. *articulus*, joint]. Affecting many joints.

pol"y·a·tom'ic [*polys;* G. *atomos*, uncut]. 1. Containing several atoms. 2. Having several hydrogen atoms replaceable by bases.

pol"y·ba'sic [*polys;* G. *basis*, base]. Applied to an acid having several hydrogen atoms replaceable by bases.

pol"y·ba'sic ac'id. Any acid which contains several replaceable hydrogen atoms.

pol'y·blast [*polys;* G. *blastos*, germ]. A free macrophage of inflamed connective tissue.

pol"y·bleph'a·ron [*polys;* G. *blepharon*, eyelid]. A supernumerary eyelid. Also called *polyblepharia, polyblephary.*

pol"y·cel'lu·lar [*polys;* L. *cellula*, small storeroom]. Having many cells.